scientific bodies have concluded that nicotine is addictive. Indeed, the tobacco industry fails to suggest any reason to believe that the current international understanding of nicotine as addictive will change in the future.

The industry's quoting of addiction experts on the importance of defining addiction is not an argument against FDA's position. It is axiomatic that whether nicotine is addictive depends on the definition of addiction. The industry fails, however, to show that nicotine would not be considered addictive under any of the current definitions of addiction.

The industry's use of an article from the *Journal of the American Medical Association* to show that the definition of addiction is imprecise is equally unpersuasive.[214] The article describes how a national panel was appointed in 1983 to try to settle variations in definitions relating to substance abuse. The panel surveyed dozens of experts from major scientific organizations and produced a consensus definition of addiction: "A chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user and continued use despite that harm."[215] This definition again is entirely consistent with the modern definition of addiction relied on by FDA, not the tobacco industry's preferred version from the 1950's.

The industry selectively quotes from several scientific publications that discuss subtle arguments over the precise definition of addiction. But these debates occur within a

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[214] Rinaldi RC, Steindler EM, Wilford BB, *et al.*, Clarification and standardization of substance abuse terminology, *Journal of the American Medical Association* 1988;259(4):555-557. *See* AR (Vol. 535 Ref. 96 vol. III.L).

[215] *Id.*

broad understanding of addiction that has garnered overwhelming consensus. This understanding universally considers nicotine to be addictive.

FDA, like many scientific and public health authorities, uses "addiction" and "dependence" interchangeably. Regardless of the terminology used, the concept that nicotine has substantial pharmacological effects on the brains of users that cause people to use tobacco compulsively is the same. Furthermore, any implication that the modern scientific understanding of addiction is motivated by public health goals, morals, or lawsuits is mistaken. As discussed in section II.A.3.b., above, the tobacco industry's preferred definition was discarded on scientific grounds in 1964, 15 years before nicotine was first considered addictive.

Thus, there is no basis upon which to conclude that FDA's finding that nicotine is addictive—a conclusion with nearly universal scientific backing—is not useful in determining whether nicotine is a "drug" under the Act. The fact that nicotine meets all currently accepted scientific definitions of a dependence-producing drug and that these definitions include as a criterion psychoactive effects on the brain is highly relevant to the Agency's inquiry.

c. General Comments on Laboratory Evidence of Addictive Potential

1. Comments from numerous health professionals and scientists agree with FDA that laboratory data in animals and humans provide compelling evidence that nicotine in cigarettes and smokeless tobacco is a pharmacologically active agent that causes addiction. For example, the American Medical Association stated that it "concurs with the scientific rationale and legal basis for the FDA proposed action," and that it "strongly supports the scientific basis regarding nicotine . . . and its essential role in maintaining demand for tobacco

products." Similarly, the Coalition on Smoking OR Health—an organization representing the American Heart Association, American Lung Association, and American Cancer Society—carefully reviewed the Jurisdictional Analysis "for accuracy, objectivity, and completeness" and concluded that "the FDA documents represent the most comprehensive, objective and scientifically accurate analysis of the impact of nicotine containing cigarettes and smokeless tobacco on the body ever conducted."

2. The tobacco industry repeatedly comments that evidence from one laboratory test *by itself* is not enough to justify the conclusion that nicotine is addictive. For example, the industry argues that positive results in drug discrimination tests in animals are not sufficient to prove that nicotine is addictive, as some nonaddictive substances also test positive. The industry repeats this same argument for subjective effects testing and animal self-administration studies. On several occasions, the industry uses quotations from addiction experts to support these arguments.

FDA agrees that evidence from each test *alone* may not prove conclusively that nicotine is addictive. But addiction authorities around the world determine whether a substance is addicting by considering results from all of the tests *together*. Nicotine tests positive in animal and human drug discrimination tests, subjective effects tests, and animal and human self-administration tests. Considering such evidence, the scientific community has overwhelmingly concluded that nicotine is addictive.

The tobacco industry's selective use of quotations from addiction experts illustrates the point. On several occasions, the industry tries to make it appear that the individuals quoted believe that addiction testing methods are not reliable or that nicotine is not addictive. In fact, these individuals are on record as reaching the opposite conclusions. For example, the

tobacco industry selectively quotes from the work of Balster that "[t]he results of self-administration studies should not be used alone for evaluating abuse potential. A number of drugs which probably possess minimal or no abuse potential have been shown to function as reinforcers in preclinical drug self-administration studies." [216] The industry also culls a quote from Woods that "[i]t should be clear that the proposition, *viz.*, that the drugs that serve as reinforcers in animals are abused by humans, is greatly oversimplified."[217] In both cases, however, the authors believe that demonstrating that a drug tests positive in both self-administration studies *and* drug discrimination studies is sufficient evidence of its abuse liability.[218] Nicotine has repeatedly proved positive in both tests.

d. Comments on Tests of Psychoactivity

1. The tobacco industry disputes FDA's analysis of drug discrimination tests in animals. The industry argues that the purpose of drug discrimination studies is merely to demonstrate that the test subject "recognizes" or "identifies" a substance that has been administered. The industry further claims that laboratory animals have been able to

[216] Balster RL, Drug abuse potential evaluation in animals, *British Journal of Addiction* 1991;86:1549-1558, at 1555. *See* AR (Vol. 8 Ref. 89).

[217] Woods J, Some thoughts on the relations between animal and human drug-taking, *Progress in Neuro-psychopharmacology and Biological Psychiatry* 1983;7:577-584, at 582. *See* AR (Vol. 535 Ref. 96, vol. III.N).

[218] Balster RL, Drug abuse potential evaluation in animals, *British Journal of Addiction* 1991;86:1549-1558, at 1555. *See* AR (Vol. 8 Ref. 89).

Woods J, Some thoughts on the relations between animal and human drug-taking, *Progress in Neuro-psychopharmacology and Biological Psychiatry* 1983;7:577-584, at 582. *See* AR (Vol. 535 Ref. 96, vol. III.N).

discriminate nicotine in the studies cited by FDA because researchers used amounts of nicotine that vastly exceed the nicotine yields in commercial cigarettes.

FDA disagrees. Drug discrimination studies are not just a measure of whether or not the subject can "recognize" or "identify" a substance; these studies assess the psychoactivity of a drug. Drugs that can be successfully discriminated from placebo are psychoactive.[219]

FDA also disagrees that animals can discriminate nicotine's stimulus properties only when receiving doses that vastly exceed those absorbed by human smokers. It is misleading to make a direct comparison between the training dose administered to animals and the nicotine yields of commercial cigarettes. Pharmacological effects elicited by a drug are the result of its plasma concentration and the amount of drug at the receptor site (i.e., site of action), not necessarily of how much drug is in the product or the amount of drug administered per kilogram of body weight. This distinction becomes critical when comparing animals with different abilities to metabolize drugs. The same amount of drug per kilogram administered to two species may lead to radically different plasma concentrations, for example, if one species breaks down and excretes the drug faster than the other.

A study by Pratt *et al.*[220] cited by the comment actually demonstrates that doses of nicotine that can be discriminated by rats yield a plasma concentration of nicotine that is comparable to the plasma concentration of nicotine in human smokers. Accordingly, rats *can* learn to discriminate a dose of nicotine physiologically comparable to the dose received by

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[219] Surgeon General's Report, 1988, at 170-171. *See* AR (Vol. 129 Ref. 1592).

[220] Pratt JA, Stolerman IP, Garcha HS, *et al.*, Discriminative stimulus properties of nicotine: further evidence for mediation at a cholinergic receptor, *Psychopharmacology* 1983;81:54-60. *See* AR (Vol. 8 Ref. 90-2).

cigarette smokers and smokeless tobacco users. Two studies by Stolerman *et al.*[221] also demonstrated that rats can discriminate from saline a dose of nicotine that is comparable to the dose delivered to human tobacco users.

2. The tobacco industry argues that nicotine's action as a discriminative stimulus is not exactly the same as that of cocaine and amphetamine.

It is well known that nicotine does not behave identically to cocaine and amphetamine in drug discrimination experiments. This difference does not mean that nicotine is not an addictive drug, however. Amphetamine, morphine, alcohol, and nicotine can all be differentiated from one another by animals and humans because of their unique effects. The fact that nicotine is not identical to cocaine is no more relevant than the fact that cocaine is not identical to morphine. What is critical is that all of these drugs are psychoactive because of their effects on the brain. The published data have shown that there are qualitative differences in these drugs' discriminative stimulus effects and that nicotine produces effects more amphetamine-like than morphine-like in animals and humans.[222] Thus, while nicotine's discriminative stimulus effects are unique, they resemble the effects of stimulants more closely than those of sedatives. These data confirm that nicotine produces critical discriminative and subjective effects shared by dependence-producing drugs.

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[221] Stolerman IP, Garcha HS, Pratt JA, *et al.*, Role of training dose in discrimination of nicotine and related compounds by rats, *Psychopharmocology* 1984;84:413-419. *See* AR (Vol. 8 Ref. 90-5).

Stolerman IP, Discriminative stimulus effects of nicotine in rats trained under different schedules of reinforcement, *Psychopharmacology* 1989;97:131-138. *See* AR (Vol. 9 Ref. 90-6).

[222] Pratt JA, Stolerman IP, Garcha HS, *et al.*, Discriminative stimulus properties of nicotine: further evidence for mediation at a cholinergic receptor, *Psychopharmacology* 1983;81:54-60. *See* AR (Vol. 8 Ref. 90-2).

Stolerman IP, Garcha HS, Pratt JA, *et al.*, Role of training dose in discrimination of nicotine and related compounds by rats, *Psychopharmocology* 1984;84:413-419. *See* AR (Vol. 8 Ref. 90-5).

3. The tobacco industry contests FDA's interpretation of three studies on drug discrimination in humans cited in the Jurisdictional Analysis. The industry concludes that there is no evidence to suggest that nicotine functions as a discriminative stimulus in humans.

Upon review of these studies and the administrative record, FDA concludes that there is convincing evidence that nicotine tests positive in human drug discrimination studies. The industry disputes the conclusion that a study by Kallman *et al.* proved that discrimination occurred in the central nervous system.[223] FDA, however, never drew this conclusion. FDA cited this study to demonstrate that smokers can differentiate between high- and low-nicotine cigarettes, a finding conceded by the industry. Much other evidence in the administrative record, described in section II.A.3.c.i. of this document and in the 1988 Surgeon General's report,[224] demonstrates that the discrimination occurs in the central nervous system.

The industry also claims that a study by Perkins *et al.* did not demonstrate discrimination.[225] Noting that male subjects identified 2 ug/kg of nicotine (administered by nasal spray) versus placebo correctly 50% of the time, the industry claims that this is exactly the percentage that would do so by chance. The industry concludes that the drug discrimination demonstrated by this study was due purely to chance and was not due to any effects of nicotine in the brain.

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[223] Kallman WM, Kallman MJ, Harry GJ, *et al.*, Nicotine as a discriminative stimulus in human subjects, in *Drug Discrimination: Applications in CNS Pharmacology*, eds. Colpaert FC, Slangen JL (Amsterdam: Elsevier Biomedical Press, 1982), at 211-218. *See* AR (Vol. 41 Ref. 89).

[224] Surgeon General's Report, 1988, at 176-178. *See* AR (Vol. 129 Ref. 1592).

[225] Perkins K, Grobe J, Scierka A, *et al.*, Discriminative stimulus effects of nicotine in smokers, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke PBS, Quik M, Thurau K, *et al.* (Basel: Birkhauser Verlag, 1994), at 111. *See* AR (Vol. 42 Ref. 111).

Upon review of the Perkins study, FDA notes that the industry has seriously misinterpreted its results. The study's objective was to determine whether subjects could differentiate the low dose of 12 ug/kg of nicotine versus placebo, and its finding was that 100% of all subjects correctly identified nicotine at this dose at least 80% of the time. The authors concluded, "These findings indicate that humans are able to discriminate among low doses of nicotine."[226] (The dose of 12 ug/kg of nicotine is less than the typical dose of nicotine received from a cigarette.[227]) Having demonstrated this finding, the authors went on to test even smaller doses to determine the lowest dose of effective discrimination, that is, the dose at which subjects discriminated nicotine at least 50% of the time. That such a dose exists does not disprove nicotine's role as a discriminative stimulus, as implied by the tobacco industry; a minimal dose that cannot be differentiated from placebo exists for *all* psychoactive drugs.

Finally, the industry contends that a study by Goldfarb *et al.* [228] is not a formal "discrimination" study. The Goldfarb study was cited not as a discrimination study but to demonstrate that humans can differentiate between cigarettes with different nicotine yields, a conclusion conceded by the industry.

4. The tobacco industry argues that studies of the "subjective effects" of nicotine have vague methods and use subjects who are not representative of all smokers. These

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[226] *Id.* at 111.

[227] Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine, *Pharmacology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

[228] Goldfarb TL, Gritz ER, Jarvik ME, *et al.*, Reactions to cigarettes as a function of nicotine and "tar," *Clinical Pharmacology and Therapeutics* 1976;19:767-772. *See* AR (Vol. 39 Ref. 53).

comments criticize a study by Henningfield *et al.*[229] which was cited by the Agency. The industry further argues that the "subjective effects" of cigarettes could be secondary to tar and cites a study to suggest that nicotine-free cigarettes cause "liking."[230] The industry thus disputes FDA's conclusion that nicotine produces subjective effects that are similar to those of other addictive drugs.

FDA disagrees. A wide range of evidence, discussed in section II.A.3.c.i., above, demonstrates that nicotine, whether administered alone or in a cigarette, behaves like other addictive drugs in "subjective effects" testing. Upon review of this evidence, FDA notes that the industry criticized only one of its cited studies.

FDA further concludes that the Henningfield study is accurate and consistent with the findings of other researchers. The study design used by Henningfield *et al.* is a standardized procedure for qualifying the abuse liability of drugs in humans; it is used nationally and internationally by addiction researchers.[231] The use of subjects with histories of drug abuse is also standard practice in such studies; indeed, as described in section II.A.3.c.i., above, these subjects are employed because they can use their history to distinguish the psychoactive effects of different drugs. Thus, for this type of abuse liability testing, it is critical that the population be composed of smokers with experience with other addictive drugs to enable them to compare the effects of nicotine to those of other drugs.

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[229] Henningfield JE, Miyasato K, Jasinski DR, Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine, *Journal of Pharmacology and Experimental Therapeutics* 1985;234:1-12. *See* AR (Vol. 39 Ref. 69).

[230] *See* section II.A.3.c.i., above, for a description of the term "liking."

[231] Jasinski DR, Henningfield JE, Human abuse liability assessment by measurement of subjective and physiological effects, in *Testing for Abuse Liability of Drugs in Humans*, eds. Fischman MW, Mello NK, NIDA Research Monograph 92 (Rockville MD: National Institute on Drug Abuse, 1989). *See* AR (Vol. 76 Ref. 172).

The results from the study by Henningfield *et al.* demonstrate that nicotine, delivered by intravenous injection or by inhalation of tobacco smoke, produces similar subjective effects. These effects include dose-related elevation in the Morphine-Benzedrine Group Scale and the "liking" scale. There is no possibility that the subjects were responding to the "flavor" of nicotine or tar when they were able to discriminate nicotine injected intravenously. Nicotine produced results similar to those of other dependence-producing drugs (e.g., morphine, cocaine, and amphetamine) on the scales used in this study.

Furthermore, researchers who preceded and followed Henningfield obtained consistent findings. Researchers other than Henningfield *et al.*, using methods other than the MBG and the "liking" scale, also confirmed that nicotine produces positive subjective effects after intranasal and intravenous administration.[232] Subjects in these studies used the following adjectives to describe the positive subjective effects of nicotine: "head rush," "feeling good," or "high." This evidence strongly demonstrates that nicotine—and not tar—is responsible for the "subjective effects" of cigarettes.

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[232] Sutherland G, Stapleton JA, Russell MAH, *et al.*, Randomised controlled trial of nasal nicotine spray in smoking cessation, *Lancet* 1992;340:324-329. *See* AR (Vol. 91 Ref. 527).

Sutherland G, Russell MA, Stapleton J, *et al.*, Nasal nicotine spray: a rapid nicotine delivery system, *Psychopharmacology* 1992;108:512-518. *See* AR (Vol. 91 Ref. 526).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine, *Pharmacology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Effects of nicotine on subjective arousal may be dependent on baseline subjective state, *Journal of Substance Abuse* 1992;4:131-141. *See* AR (Vol. 348 Ref. 5516).

Johnston LM, Tobacco smoking and nicotine, *Lancet* 1942;2:742. *See* AR (Vol. 278 Ref. 3947).

Jones RT, Farrell TR III, Herning RI, Tobacco smoking and nicotine tolerance, in *Self-Administration of Abused Substances: Methods for Study,* ed. Krasnegor NA, NIDA Research Monograph 20 (Rockville MD: National Institute on Drug Abuse, 1978), at 202-208. *See* AR (Vol. 41 Ref. 88).